AD-A119 354 STANFORD UNIV CA DEPT OF STATISTICS F/G 12/1
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BY

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TECHNICAL REPORT NO. 18
JULY 1982

PREPARED UNDER CONTRACT
N00014-77-C-0306 (NR-042-373)
FOR THE OFFICE OF NAVAL RESEARCH

DEPARTMENT OF STATISTICS
STANFORD UNIVERSITY
STANFORD, CALIFORNIA

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Technical Report No. 18

July, 1982

Prepared Under the Auspices
of
Office of Naval Research Contract
N00014-77-C-0306 (NR-042-373)

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ALLOCATION RULES FOR SEQUENTIAL CLINICAL TRIALS

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Consider the following simplified model of a clincial trial. Patients arrive sequentially at a treatment center and receive one of two treatments: A or B. The (immediate response of the i^{th} patient to receive treatment A is x_i, $i = 1,2,\ldots$, that of the j^{th} patient to receive treatment B is y_j, $j = 1,2,\ldots$. At any stage of the process, having observed $x_1,\ldots,x_m$, $y_1,\ldots,y_n$, the experimenter can stop the experiment and declare (1) A is the better treatment, (2) B is better, or (3) there is essentially no difference between A and B; or he can continued the experiment and assign the next patient to treatment A or B according to some allocation rule. In this paper we shall be primarily interested in the experimenter's allocation rule, which should be selected insofar as possible (i) to permit valid inferences upon termination of the experiment and (ii) to minimize in some sense the number of patients receiving the inferior treatment during the course of the experiment.

The specific mathematical framework developed below to discuss this problem was introduced by Flehinger, Louis, Robbins, and Singer (1972) and developed by Robbins and Siegmund (1973), Louis (1975), and Hayre (1979). To a considerable extent the present paper is a review and exposition of these ideas. An interesting and somewhat different approach has been recently developed by Bather (1980, 1981), and it would be interesting to make a systematic comparison of Bather's approach with that outlined below.

We assume that $x_1,\ldots,x_m,\ldots$ are independent $N(\mu_1,1)$ and $y_1,\ldots,y_n,\ldots$ are independent $N(\mu_2,1)$ random variables, and that the x's and y's are independent. For an indication how the results given here can be extended via large sample approximations to non-normal data, see Robbins (1974). Let $\delta = \mu_1 - \mu_2$, and to be specific assume that the better treatment is that yielding the larger mean response. Hence to say that treatment A is superior to say that $\delta > 0$, etc.

Let $\bar{x}_m = m^{-1}\sum_{i=1}^{m} x_i$, $\bar{y}_n = n^{-1}\sum_{j=1}^{n} y_j$, and $z_{m,n} = \frac{mn}{m+n}(\bar{x}_m - \bar{y}_n)$. Having observed $x_1,\ldots,x_m$ and $y_1,\ldots,y_n$, the natural estimator of δ is $\hat{\delta}_{m,n} = \bar{x}_m - \bar{y}_n$. Since problems of statistical inference about δ are invariant under changes in location of the data, it is reasonable to consider invariant procedures, i.e. those based on the process $z_{m,n}$, $m,n \geq 1$ or equivalently on $u_i = x_i - x_1$, $i = 1,2,\ldots$ and $v_j = y_j - x_1$, $j = 1,2,\ldots$. Our first result is a "separation" theorem, which says that in a certain sense the problem of statistical inference about δ can be separated from the problem of allocation, provided we restrict ourselves to invariant procedures (cf. Lemma 1 of Robbins and Siegmund, 1973).

It is convenient to introduce the following notation:

$$\mathcal{F}_{m,n} = \mathcal{B}(u_i,\ i \leq m;\ v_j,\ j \leq n) ,$$

$W(t)$ = Brownian motion with drift δ ,

$\mathcal{F}_W(t) = \mathcal{B}(W(s),\ s \le t)$,

$t_{m,n} = mn/(m+n)$.

Proposition 1. For arbitrary $m,n \ge 1$

$$\mathcal{L}(z_{m+1,n} - z_{m,n} | \mathcal{F}_{m,n}) = \mathcal{L}(W(t_{m+1,n}) - W(t_{m,n}) | \mathcal{F}_W(t_{m,n}))$$

and

$$\mathcal{L}(z_{m,n+1} - z_{m,n} | \mathcal{F}_{m,n}) = \mathcal{L}(W(t_{m,n+1}) - W(t_{m,n}) | \mathcal{F}_W(t_{m,n})) .$$

Proof. Simple algebra yields

$$(1) \qquad z_{m+1,n} - z_{m,n} = nx_{m+1}/(m+n+1) - n(\sum_1^n y_j + \sum_1^m x_i)/(m+n)(m+n+1) .$$

It is easy to see that the two terms on the right hand side of (1) are each uncorrelated with u_i, $i \le m$ and v_j, $j \le n$. Hence by properties of the normal distribution $z_{m+1,n} - z_{m,n}$ given $\mathcal{F}_{m,n}$ is normally distributed with expectation

$$n\mu_1/(m+n+1) - n(m\mu_1 + n\mu_2)/(m+n)(m+n+1)$$

$$= n^2\delta/(m+n)(m+n+1) = \delta(t_{m+1,n} - t_{m,n})$$

and variance

$$[n/(m+n+1)]^2 + n^2/(m+n)(m+n+1)^2 = t_{m+1,n} - t_{m,n} .$$

But this is precisely the conditional distribution of $W(t_{m+1,n}) - W(t_{m,n})$ given $\mathcal{F}_W(t_{m,n})$. A similar argument applies to $z_{m,n+1} - z_{m,n}$.

Corollary 1. For any invariant allocation rule the processes

$$\{z_{m,n} - mn/(m+n),\ \mathcal{F}_{m,n}\}$$

and

$$\{(z_{m,n} - mn/(m+n))^2 - mn/(m+n),\ \mathcal{F}_{m,n}\}$$

are martingales.

An important consequence of Proposition 1 is that for any allocation rule based on the process $z_{m,n}$ or equivalently on the u's and v's, there exists an "isomorphic" allocation rule based on $W(t_{m,n})$ such that the sequences of pairs

$\{z_{m,n},\ mn/(m+n)\}$ and $\{W(t_{m,n}),\ t_{m,n}\}$ have the same joint distribution. Hence if $0 < t_f \leq \infty$ various allocation rules yield sequences of "observations" $W(t_{m,n})$, $0 < t_{m,n} \leq t_f$, which differ only in the (random) times at which the Brownian path is observed. Because the Brownian paths are continuous and the increments $t_{m+1,n} - t_{m,n}$ or $t_{m,n+1} - t_{m,n} \in (0,1)$, the exact choice of allocation rule has a limited effect on the joint distribution of the observed data provided $t_{m,n} \to t_f$ as $m+n \to \infty$. In particular, if the process $\{W(t_{m,n}),\ t_{m,n}$ is observed until it first leaves some region with a continuous boundary in the space time plane, the point at which the process leaves the region has a distribution which is approximately independent of the allocation rule.

For our present purposes this has the following consequences. Assume temporarily that the allocation rule does not depend on the data -- for example that observations are taken in pairs (x_i,y_i), $i = 1,2,\ldots$ and $w_i = x_i - y_i$. Assume also that in this context we favor a particular proceudre for making inferences about $\delta = Ew_i$. For example, to test H_0: $\delta = 0$ we stop sampling at $\min(T,2\nu)$, where

$$T = \inf\{n: \left|\sum_1^n w_i\right| \geq 2b\}$$

and ν is some positive integer. If $T \leq 2\nu$ and $\Sigma_1^T w_i \geq 2b$ we reject H_0 and say that $\delta > 0$; if $T \leq 2\nu$ and $\Sigma_1^T w_i \leq -2b$ we reject H_0 and say that $\delta < 0$; if $T > 2\nu$ we accept H_0 as being approximately true. The power function of this test of H_0: $\delta = 0$ against H_1: $\delta \neq 0$ is $P_\delta\{T \leq 2\nu\}$ and the expected sample size is $E_\delta(T \wedge 2\nu)$. For any invariant allocation rule there exists the analogous procedure: stop sampling when $mn/(m+n) \geq \nu$ or at

$$(\tilde{M},\tilde{N}) = \inf\{(m,n): |z_{m,n}| \geq b\} \ ,$$

whichever occurs first, and reject H_0: $\delta = 0$ if and only if $\tilde{M}\tilde{N}/(\tilde{M}+\tilde{N}) \leq \nu$. It follows from the remarks following Proposition 1 that the power function $P_\delta\{\tilde{M}\tilde{N}/(\tilde{M}+\tilde{N}) \leq \nu\}$ of this test satisfies

$$P_\delta\{\tilde{M}\tilde{N}/(\tilde{M}+\tilde{N}) \leq \nu\} \cong P_\delta\{T \leq 2\nu\} \ , \tag{2}$$

and

$$2E_\delta\{[\tilde{M}\tilde{N}/(\tilde{M}+\tilde{N})] \wedge \nu\} \cong E_\delta(T \wedge 2\nu) \ . \tag{3}$$

Hence we have obtained a sequential test whose power function is to a considerable extent independent of the allocation rule used, and we are free to consider different allocation rules in an attempt to minimize the number of observations taken on the inferior treatment.

Note that although we proceed with the discussion for one particular sequential test, we could equally well consider others, e.g. a repeated significance test.

Before we consider in detail the choice of allocation rule, it is helpful to observe the following limits imposed by (3). Let M and N denote the number of x and y observations respectively when sampling stops, so $MN/(M+N) \cong [\tilde{M}\tilde{N}/(\tilde{M}+\tilde{N})] \wedge \nu$. Since $\min(M,N) \geq MN/(M+N)$ with equality if and only if $\max(M,N) = \infty$, it follows from (3) that

$$\min(E_\delta M, E_\delta N) \geq \tfrac{1}{2} E_\delta(T \wedge 2\nu) \quad , \tag{4}$$

and a necessary condition for approximate equality in (4) is that $\max(E_\delta M, E_\delta N)$ be extremely large. Since $x(1-x) \leq 1/4$ with equality if and only if $x = 1/2$, by (3)

$$E_\delta(M+N) \geq 4E_\delta\{MN/(M+N)\} \cong 2E_\delta(T \wedge 2\nu) \tag{5}$$

and there is equality in (5) if and only if M and N are approximately equal with probability one. From (4) and (5) we conclude that the expected number of observations on the inferior treatment is at least $1/2$ as large as pairwise allocation requires; and any deviation from pairwise allocation results in some increase in the total expected sample size.

The following argument for choosing an allocation rule is due to Hayre (1979). Suppose that when δ is the true difference in mean response, the cost to the experimenter of an x observation is $g(\delta)$ while that of a y observation is $h(\delta)$. Hence the total expected cost of sampling is

$$g(\delta)E_\delta(M) + h(\delta)E_\delta(N) \quad . \tag{6}$$

The overall risk function is the sum of (6) and the risk associated with making a wrong terminal decision. But since the power function of our test is essentially independent of the allocation rule used, we can ignore the terminal decision part of the risk function and attempt to minimize (6). Since

$$M = [MN/(M+N)](1+M/N) = [MN/(M+N)](1+Q) \quad , \tag{7}$$

say, and

$$N = [MN/(M+N)](1+Q^{-1}) \quad , \tag{8}$$

we can rewrite (6) as

$$[h+g]E_\delta[MN/(M+N)] + E_\delta\{[MN/(M+N)]\{gQ+hQ^{-1}\}\} \quad . \tag{9}$$

Moreover, by (3) the first term in (9) is essentially independent of the allocation rule, so we attempt to minimize the second. Calculus shows that for every Q $gQ + hQ^{-1} \geq 2(gh)^{1/2}$ with equality if and only if

$$Q = (h/g)^{1/2} \quad . \tag{10}$$

Hence a lower bound to (9) is

$$(h^{1/2} + g^{1/2})^2 \, E_\delta[MN/(M+N)] \quad , \tag{11}$$

which could be achieved only if we could allocate observations so that

$$P_\delta\{N/M = [g(\delta)/h(\delta)]^{1/2}\} = 1 \quad . \tag{12}$$

Since δ is unknown this is impossible, but as an approximation we consider the allocation rule which takes the next observation from the y population if and only if

$$n/m < [g(\bar{x}_m - \bar{y}_n)/h(\bar{x}_m - \bar{y}_n)]^{1/2} \quad . \tag{13}$$

To the extent that this allocation rule behaves as we hope it will, i.e. to the extent that (12) is approximately true, by (7) and (8) we have the approximations

$$E_\delta(M) \cong E_\delta[MN/(M+N)][1 + (h/g)^{1/2}] \quad , \tag{14}$$

$$E_\delta(N) \cong E_\delta[MN/(M+N)][1 + (g/h)^{1/2}] \quad , \tag{15}$$

and the risk (6) is approximately the lower bound (11).

A numerical example illustrating these results is given in Table 1. The functions g and h are of the form

$$g(\delta) = h(-\delta) = \begin{cases} 1 & \text{if} \quad \delta > 0 \\ 1 + d|\delta| & \text{if} \quad \delta < 0 \end{cases} \quad . \tag{16}$$

This choice has the interpretation that the basic (experimental) cost of an observation is unity, and the additional (ethical) cost of assigning the inferior treatment is proportional to $|\delta|$. For comparison the first row in each cell of Table 1 is for pairwise allocation, and the computations of power and expected sample size use the approximations suggested by Siegmund (1979) and shown to be very accurate. The second row of each cell gives results for the sampling rule (13) with g and h defined by (16). The first entry is the outcome of a 400 repetition Monte Carlo experiment, and

the parenthetical entry is the theoretical approximation given by (15), (14), or (11). The Monte Carlo results lend support to our informal interpretation of Proposition 1 to the effect that the power and $E_\delta[MN/(M+N)]$ are approximately independent of the allocation rule, and they indicate that the approximations (15), (14), and (11) are quite good. Hayre (1979) reached the same conclusions for a different stopping rule and value of d in (16). Most importantly the results show a fairly substantial decrease in risk of about 15-30% when the allocation rule (13) is used.

TABLE 1

First row in each cell is for pairwise allocation; second row is for allocation rule (13) with h and g given by (16) with $d = 20$; in all cases $b = 10.8$, $\nu = 25$; theoretical calculations are in parentheses; others are Monte Carlo

δ	Power	$E_\delta(N)$	$E_\delta(M)$	$2E_\delta[MN/(M+N)]$	Risk
1.13	(1.00)	(19.9)	(19.9)	(19.9)	(490)
	1.00	12.3 (12.0)	53.7 (58.3)	20.0	343 (341)
.85	(.986)	(26.4)	(26.4)	(26.4)	(502)
	.995	15.9 (16.9)	62.7 (59.7)	25.2	349 (363)
.57	(.788)	(36.8)	(36.8)	(36.8)	(493)
	.793	24.0 (23.6)	77.5 (83.2)	36.3	375 (376)
.28	(.279)	(46.7)	(46.7)	(46.7)	(355)
	.298	36.4 (32.5)	77.4 (83.5)	46.6	318 (298)
.00	(.050)	(49.5)	(49.5)	(49.5)	
	.048	54.1	56.3	49.6	

The reduction in risk of 15-30% compared to pairwise sampling in Table 1 makes the allocation rule (13) seem attractive; but it is not large enough to overwhelm certain disadvantages without further investigation. (By way of comparison a fixed sample size with paired observations requires 48 pairs to achieve about the same power function as in Table 1. This leads to risks of 1181 and 912 for $\delta = 1.13$ and .85, so sequential sampling with pairwise allocation leads to a reduction in risk for large $|\delta|$ of about 50% compared to a fixed sample.) The disadvantages include (i) the fact that the allocation rule (13) is non-randomized, (ii) questionable performance when the patient population is stratified, (iii) difficulty in implementation if the data are examined occasionally, but not continuously, and (iv) questionable performance for survival data, where treatment assignments must be made for new patients before data

become available on old ones. Accommodating these difficulties leads to some deterioration in the performance of adaptive allocation rules, which may lead to questioning their desirability at all. Here we discuss (i) and (ii) by means of a Monte Carlo experiment.

The advantages of randomization in clinical trials has been discussed at great length-primarily in an effort to eliminate selection bias (e.g. Blackwell and Hodges, 1957), but secondarily to provide the possibility of a permutation test of the hypothesis of no treatment effect. It is easy to define a randomized version of (13) to cut down on selection bias. For example, we might select treatment B or treatment A with relative probabilities given by the right hand side of (13). More precisely, let

$$\lambda_{m,n} = [g(\bar{x}_m - \bar{y}_n)/h(\bar{x}_m - \bar{y}_n)]^{1/2}$$

and take the next observation from the y population if and only if

$$U_{m+n+1} \leq \lambda_{m,n}/(1+\lambda_{m,n}) \quad , \tag{17}$$

where $U_1, U_2, \ldots$ is an auxiliary sequence of independent uniform random variables which we generate. Asymptotically this rule generates the appropriate relative frequencies of treatment selections. A more sophisticated version would be one which takes account of how far n/m is from the desired ratio of $\lambda_{m,n}$ in selecting the next treatment. For g and h given by (16) with $d = 20$, and for δ in the range $[-1,1]$, the right hand side of (17) is in the range $(.1,.9)$ with high probability, so there is always some indeterminacy in the next treatment assignment.

TABLE 2

Randomized Allocation (17)

$b = 10.8$, $\nu = 25$, g and h given by (16) with $d = 20$

δ	Power	$E_\delta(N)$	$E_\delta(M)$	$2E\,[MN/(M+N)]$	Risk
1.13	1.00	12.7	50.3	19.5	350
.85	.995	18.2	60.3	26.8	388
.57	.793	26.6	72.4	37.0	402
.28	.315	38.8	72.0	46.0	328

Table 2 gives the outcome of a 400 replication Monte Carlo experiment using the randomized allocation rule (17). By comparison with Table 1 we see that randomization has led consistently to an increase in risk, but one so slight that the benefits of randomization seem to outweigh the liability.

The question of stratification is more complicated because the results may depend on the number and relative sizes of different strata. The difficulties are most acute with a large number of small strata, where one usually wants to guarantee a certain amount of balance in the sample from each stratum, so that a stratum could be analyzed by itself if the model relating different strata seems to be inappropriate.

To be specific suppose there are r strata and for $k = 1,2,\ldots,r$, in stratum k the response of the i^{th} patient on treatment A is x_{ki}, which is distributed $h(\mu_k + \delta,1)$, and that of the j^{th} patient on treatment B is y_{kj}, distributed $h(\mu_k,1)$. After m_k assignments of treatment A and n_k of treatment B in the k^{th} stratum, the maximum likelihood estimator of the treatment effect δ is (in the obvious notation)

$$\hat{\delta}(\underline{m},\underline{n}) = \frac{\sum_{k=1}^{r} \frac{m_k n_k}{m_k + n_k} (\bar{x}_{k,m_k} - \bar{y}_{k,n_k})}{\sum_{k=1}^{r} \frac{m_k n_k}{m_k + n_k}} \tag{18}$$

Let $z(\underline{m},\underline{n})$ denote the numerator and $t(\underline{m},\underline{n})$ the denominator of $\hat{\delta}(\underline{m},\underline{n})$.

It is easy to obtain a result analogous to Proposition 1, and hence to conclude that $z(\underline{m},\underline{n})$ behaves like Brownian motion with drift δ in the time scale of $t(\underline{m},\underline{n})$ provided that an invariant treatment allocation rule is used. Here invariant means that the choice of the next treatment assignment may depend only on the vector of differences $(\bar{x}_{1,m_1} - \bar{y}_{1,n_1}, \ldots, \bar{x}_{r,m_r} - \bar{y}_{r,n_r})$. Hence as above we can test $\delta = 0$ with a test whose power function is essentially independent of the (invariant) allocation rule used, and we can turn our attention to the cost of sampling.

In analogy with (6) suppose the expected cost of sampling is given by

$$g(\delta)\Sigma\mathbb{E}M_k + h(\delta)\Sigma\mathbb{E}N_k \quad , \tag{19}$$

where M_k (N_k) is the number of x's (y's) observed in the k^{th} stratum, $k = 1,2,\ldots,r$. The argument leading to (11) now gives as a lower bound to (19)

$$(h^{1/2} + g^{1/2})^2 E_\delta[\sum_{k=1}^{r} M_k N_k/(M_k + N_k)] \tag{20}$$

and there is equality between (19) and (20) if and only if (cf. (12))

$$P_\delta\{N_k/M_k = [g(\delta)/h(\delta)]^{1/2}\} = 1 \quad \text{for all} \quad k = 1,\ldots,r \quad . \tag{21}$$

This suggests in analogy with (13) that if a new patient arrives and falls into stratum k, then he is assigned treatment B if and only if

$$n_k/m_k < [g(\hat{\delta}(\underline{m},\underline{n}))/h(\hat{\delta}(\underline{m},\underline{n}))]^{1/2} \tag{22}$$

where $\hat{\delta}$ is given in (18).

However, there is an additional practical consideration, which is especially important when there are small strata. The model of fixed treatment effect across strata is somewhat tentative and usually must be checked. To do this requires a minimal amount of balance in the assignment of treatments in each stratum individually. Hence we modify the sampling rule (22) by choosing some small positive number ν_0, and use (22) only if $m_k n_k/(m_k+n_k) \geq \nu_0$. If $m_k n_k/(m_k+n_k) < \nu_0$, we make the treatment assignment in some way that provides for about half of the first $4\nu_0$ patients to receive one treatment and half the other. Of course, this effects our ability to approximate (21), especially in small strata where the threshold ν_0 may not be exceeded; but it avoids the disastrous situation where almost all assignments in a small stratum are to one treatment.

Table 3 reports the results of a Monte Carlo experiment to determine the effects of stratification together with randomization. The test is defined by the same parameters as those in Tables 1 and 2, and hence has essentially the same power function. There are four strata in the relative sizes 4:3:2:1. The threshold is $\nu_0 = 3$, and strict pairwise sampling is used in each stratum until this threshold is reached. Thereafter a randomized version of (21) as specified in (17) is used.

The results are more ambiguous than in Table 2. For large $|\delta|$ stratification substantially increases the risk to the extent that sequential data dependent allocation seems only slightly better than pairwise sampling. For small $|\delta|$ there is a comparatively insignificant increase in risk. Although these results are not surprising qualitatively, and therefore probably persist to some extent under different

TABLE 3

Stratified Data, Randomized Allocation

$b = 10.8$, $\nu_0 = 3$, $\quad = 25$, $d = 20$

δ	Power	$\sum_k E_\delta(N_k)$	$\sum_k E_\delta(M_k)$	$2\sum_k E_\delta[M_k N_k/(M_k+N_k)]$	Risk
1.13	1.00	17.6	23.8	19.8	439
.85	.990	22.3	35.1	26.6	449
.57	.848	29.2	47.8	35.2	409
.28	.288	40.3	61.1	46.9	327

experimental conditions, the exact magnitude of the changes may well be sensitive to the number and size of the strata, the parameters b, ν_0, ν, etc.

A conclusion to be drawn from Tables 2 and 3 is that practical constraints on using an allocation rule like (13) may reduce the advantage over pairwise allocation exhibited in Table 1, and suggest that some study of those constraints relevant to a

particular problem should probably be made before seriously contemplating use of a sequential allocation scheme.

Remarks (i). It seems to be an interesting mathematical problem to explain the success exhibited in Table 1 for the approximations (14) and (15). Heuristic arguments indicate that these approximations should be valid to within $0(1)$ as $b \to \infty$, $\nu \to \infty$, and $b\nu^{-1} \to$ const. But proving this result or, what is more interesting, determining the constant implicit in the $0(1)$ may be rather difficult.

(ii) A challenging problem is to extend Proposition 1 and its consequences to other situations. An interesting discussion by Jennison, Johnstone, and Turnbull (1981) shows that the naive generalization to three populations is not valid.

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1. REPORT NUMBER: 18	2. GOVT ACCESSION NO.: AD-A119 354	3. RECIPIENT'S CATALOG NUMBER:
4. TITLE (and Subtitle): ALLOCATION RULES FOR SEQUENTIAL CLINICAL TRIALS		5. TYPE OF REPORT & PERIOD COVERED: TECHNICAL REPORT
		6. PERFORMING ORG. REPORT NUMBER:
7. AUTHOR(s): D. SIEGMUND		8. CONTRACT OR GRANT NUMBER(s): N00014-77-C-0306
9. PERFORMING ORGANIZATION NAME AND ADDRESS: DEPARTMENT OF STATISTICS STANFORD UNIVERSITY, STANFORD, CALIF.		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: NR-042-373
11. CONTROLLING OFFICE NAME AND ADDRESS: Statistics & Probability Program Code (411(SP) Office of Naval Research Arlington, Va. 22217		12. REPORT DATE: July 1982
		13. NUMBER OF PAGES: 10
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report): UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE:

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APPROVED FOR PUBLIC RELEASE: DISTRIBUTION UNLIMITED.

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ADAPTIVE ALLOCATION, SEQUENTIAL CLINICAL TRIALS

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TECHNICAL REPORT NO. 18

ALLOCATION RULES FOR SEQUENTIAL CLINICAL TRIALS

ABSTRACT

The work of Flehingher, Louis, Robbins, and Singer (Proc. Nat. Acad. Sci. U.S.A., 1972), Robbins and Siegmund (JASA, 1974), Louis (Biometrika, 1975), and Hayre (Biometrika, 1979) is reviewed. Variations of the basic model, including stratification and randomized allocation, are considered, and the results of some simulations presented.